REMARKS

Status Summary

Claims 1-20 are pending. Claims 1-14 are withdrawn as directed to a non-elected invention and are hereby cancelled. Claims 15-20 were examined on the merits considering the species elected by the applicant, which the examiner states is free of the prior art. The examiner then selected an additional species for examination on the basis that none of the claims are drawn uniquely to the elected species. Claims 15-20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 15 and 20 are further rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,552,007 or U.S. Patent Application Publication No. 2002-0094964. Reconsideration in view of the claim cancellation and amendments and the following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 15-20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, the examiner states that claim 15 is vague because it is unclear whether the therapeutic agent to which A is bound via a thiol linkage includes the naturally occurring or synthetic somatostatin peptide or fragment B. Official action, page 3.

In response, claim 15 is amended to specify that a somatostatin analog administered to a subject includes (A – B) and a therapeutic agent bound via a thiol linkage to A. Accordingly, it is respectfully requested that the rejection of claim 15 under 35 U.S.C. § 112, second paragraph, be withdrawn. Claims 16-20 ultimately depend from claim 15, and therefore, it is requested that the rejection of these claims also be withdrawn.

Rejection of Claim Under 35 U.S.C. § 103(a)

Claims 15 and 20 are further rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,552,007 to Chen et al. or U.S. Patent Application Publication No. 2002-0094964 to Chen et al., which is the publication of the application issued as the '007 patent (hereinafter collectively referred to as "Chen"). The examiner states that Chen describes a somatostatin analog of the formula (A-B), which includes a therapeutic agent, a cysteine residue

A, and a somatostatin peptide B, wherein the therapeutic agent is bound via a thiol linkage to A. As a specific example, Chen describes a method of selectively killing cancer cells in a cell culture comprising contacting cells with the somatostatin binding agent octreotide (D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr(ol), which is conjugated to paclitaxel via a thiol linkage. The examiner further identifies cancer as an SSTR-associated disease, relying on the disclosure of the instant application. Although Chen does not teach direct administration of the somatostatin analog to a subject, the examiner contends that such administration would have been obvious to one of skill in the art at the time the invention was made and could be performed with a reasonable chance of success in treating cancer based upon the *in vitro* results of Chen. Official action, pages 3-6.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. § 2142.

In determining if there is obviousness in the first instance, "it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *See* M.P.E.P. § 2142.

In response to the foregoing rejection, applicant initially responds that claim 15 is amended to specify that the somatostatin analog comprises a therapeutic agent bound to an interior cysteine of the cysteine-containing peptide A. Support for the amendment can be found in the originally filed specification, including for example, at page 8, lines 2-7, wherein it is described that an interior site for thiol-mediated attachment, refers to (1) a site other than at the

carboxyl or amino terminus of the molecule, or (2) a thiol group of a terminal cysteine, wherein the terminal amino or carboxyl group is blocked from derivatization. Claim 20 depends from claim 15, and therefore includes all of the elements of claim 15, including thiol linkage at an interior cysteine of the cysteine-containing peptide A.

In view of amended claim 15, applicant further responds that a *prima facie* case of obviousness has not been made because (1) Chen does not describe all the elements of claims 15 and 20, and (2) there is not any suggestion or motivation to modify the teachings of Chen to thereby obtain the claimed invention.

Chen describes somatostatin analogs of the general formula X-spacer-NH-peptide, wherein X is an anticancer drug and the peptide is a somatostatin binding agent such as octreotide, lanreotide, or vapreotide. Chen summarizes the disclosed somatostatin analogs as follows:

> In general, this invention employs somatostatin analogs having sequence of X-c[Cys-Phe-Trp-Lys-Thr-Cys]-X, X-c[-Cys-Tyr-D-Trp-Lys-Val-]-X, or X-c[Cys-Phe-D-Trp-Lys-Thr-Cys]-X to provide a new system for delivering anti-cancer drugs to the cancer cells. The synthesis of somatostatin analogs is preferably performed on a solid-phase peptide synthesizer using Fmoc chemistry. The desired compound, such as anticancer drugs paclitaxel, doxorubicin or camptothecin or the like, that is intended to be delivered to the target cells, reacts with a spacer (preferably having a carboxyl terminal group) to form a covalent bond, resulting in a drug-spacer complex. Such complex is then coupled to the N-terminal of the somatostatin analog peptide on the resin to form the final product, namely, a drug-spacer-peptide complex, as shown in FIG. 1. The present invention further provides a method of synthesizing a DOPE-PEG-spacer-somatostatin analog complex, which is useful for the preparation of a liposome drug delivery system, as shown in FIG. 1. (Col. 1, lines 47-67)

Based upon the description of Chen, the somatostatin analogs described therein include a drug or therapeutic agent (X) that is bound to a spacer molecule, *i.e.*, a drug-spacer complex, which is then coupled to the N-terminal of the somatostatin peptide. Chen further describes that, in the preferred embodiment, the desired compound X is linked with one of two carboxylic acid groups of a dicarboxylic acid spacer, such as glutaric acid, while the somatostatin peptide is linked with the other. *See* col. 2, lines 66, through col. 3, line 8; col. 3, lines 33-42.

Chen also describes three spacer molecules having a –SH group. In two examples, the –SH group may be reacted with X4, a drug component that has a maleimide group for forming a

covalent bond. *See* col. 4, lines 27-32 and 61-63. In a third example, the –SH group may be reacted with a maleimide-containing compound Y3, which is CH_3-O-(-CH_2CH_2O-)$_m$-CH_2CH_2-maleimide, where m=45-225. In each case, a thiol linkage between the drug and the spacer molecule in the depicted somatostatin analog is positioned at a terminal residue of the spacer. Thus, in contrast to the somatostatin analogs of the present invention, the analogs described by Chen include a drug to the spacer molecule via a thiol linkage to a terminal residue of the spacer.

Chen also does not describe preparation of a cysteine-containing peptide A wherein the terminal amino or carboxyl group is blocked from derivatization. Rather, the somatostatin analog described by Chen and identified by the examiner (*see* col. 5, lines 10-30, of U.S. Patent No. 6,552,007) expressly includes a derivatized terminal amino group. This example depicts a drug-spacer-somatostatin molecule having a free $-NH_2$ group for further connection to an additional component, R, for improving water solubility.

Based upon the foregoing, the somatostatin analogs of Chen clearly differ from the somatostatin analogs of the present invention in that the thiol linkage between the drug and cysteine-containing spacer molecule is not at an interior cysteine residue, as defined in the instant application. In addition, Chen does not motivate or suggest preparation of thiol conjugation at a non-terminal or interior site. Rather, the somatostatin analogs disclosed by Chen suggest just the opposite (*e.g.*, the above-noted molecule for improved solubility). The disclosed advantages of drug attachment at an interior site of the cysteine-containing peptide, for example improved stability, are also not described or suggested by the cited art.

Based upon the amendment of claim 15 and the foregoing remarks, a prima facie case of obviousness has not been made. Therefore, it is respectfully requested that the rejection of claims 15 and 20 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, she is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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